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㉒ Cimetidine pharmaceutical compositions.

㉓ Delayed-release oral dosage forms are described comprising cimetidine or a salt thereof and  
optionally a buffer that is capable of aiding dissolution of cimetidine in the intestine, coated with a  
release-delaying substance comprising a coating agent such as Eudragit<sup>R</sup> L 30 D.

## PHARMACEUTICAL COMPOSITIONS

This invention relates to solid pharmaceutical compositions containing cimetidine and methods for their preparation.

Cimetidine is a histamine H<sub>2</sub>-antagonist which has been described in U.K. Patent Specification 1,397,436. 5 Cimetidine has been shown to be useful in the treatment of duodenal, gastric, recurrent and stomal ulceration, and reflux oesophagitis and in the management of patients who are at high risk from haemorrhage of the upper gastro-intestinal tract.

Cimetidine has been made available to patients in a variety of dosage forms; for example tablets, granules, syrups and suspensions. In most, if not all, of these dosage forms, the cimetidine is in an immediate-release 10 form; that is to say the nature of the formulation is such that by the time the cimetidine leaves the stomach, it is either in solution or is in the form of a suspension of fine particles, i.e. a form from which it can be readily absorbed.

Coating agents which prevent release of an active ingredient in the stomach but which allow release in the intestines are known as enteric coating agents and many such substances are known in the art for this purpose. 15 However, it has been found that, when many such release-delays substances are used in conjunction with cimetidine, although release is delayed, the bioavailability of the cimetidine is substantially reduced.

In order to test the bioavailability of a given formulation, it is generally necessary to conduct the tests in human volunteers or animals and such tests are thus both time consuming and expensive. In order to provide a cheaper and more convenient means of testing bioavailability, *in vitro* tests have now been developed. These 20 tests can predict accurately good bioavailability of delayed-release forms of cimetidine. The requirements for these tests have been determined from extensive human bioavailability studies.

In a first aspect, the present invention provides a delayed-release oral dosage form comprising cimetidine or a pharmaceutically acceptable acid addition salt thereof, coated with a release-delaying substance which does not permit more than 10% release of cimetidine after 2 hours in 0.1 N hydrochloric acid and which satisfies 25 each of the following dissolution tests (a) to (c) in a European Pharmacopoeia apparatus, with rotating paddle, 100 revolutions per minute, at 37°C with 800 ml of buffered aqueous dissolution medium comprising sodium hydroxide and 0.04 moles of monopotassium phosphate:—

T	Conditions	% Release of Cimetidine	
		Formulae with Cimetidine base	Formulae with a pharmaceutically acceptable acid addition salt of cimetidine.
E	After 2 hours in 0.1 N hydro-chloric acid and a further time in dissolution medium at pH 5.7, 6.0 or 6.8		
(a)	5.7	Minimum 85% after 2 hours	Not applicable
(b)	6.0	Minimum 75% after 1 hour	Minimum 75% after 2 hours
(c)	6.8	Minimum 90% after 45 mins.	Minimum 80% after 45 mins.

For dosage forms comprising a pharmaceutically acceptable acid addition salt of cimetidine it has been

found to be unnecessary to conduct test (a) in order to predict good bioavailability. Accordingly, the expression "not applicable" has been inserted into the right hand column of test (a) in the above-noted table.

The dosage forms of this invention can be used to extend the duration of action of cimetidine as well as maintaining good bioavailability with plasma levels greater than the therapeutically effective concentration of 0.5 mg/l. Maintaining such plasma levels, which result in substantial suppression of acid secretion, for extended periods of time increases the rate of healing in gastric or duodenal ulceration and is advantageous in disease states such as gastroesophageal reflux disease, dyspepsia or stress ulceration where prolonged control of acid secretion is desirable.

Preferably the dosage forms of this invention also comprise a buffer that is capable of aiding dissolution of cimetidine in the alkaline environment of the intestine.

Thus in a second aspect this invention provides a delayed-release oral dosage form comprising cimetidine or a pharmaceutically acceptable acid addition salt thereof and a buffer that is capable of aiding dissolution of cimetidine in the intestine, coated with a release-delaying substance which does not permit more than 10% release of cimetidine after 2 hours in 0.1 N hydrochloric acid and which satisfies each of the following dissolution tests (b) and (c) in a European Pharmacopoeia apparatus, with rotating paddle, 100 revolutions per minute, at 37°C with 800 ml of buffered aqueous dissolution medium comprising sodium hydroxide and 0.04 moles of monopotassium phosphate :—

		Conditions	t Release of Cimetidine
T	E	S	T
	After 2 hours in 0.1 N hydrochloric acid and a further time in dissolution medium at pH 6.0 or 6.8	Formulae with cimetidine or a pharmaceutically acceptable acid addition salt thereof and a buffer.	
(b)	6.0		Minimum 50% after 2 hours
(c)	6.8		Minimum 85% after 1 hour

The preferred embodiments of this invention which comprise cimetidine together with a buffer give reproducible bioavailability with minimal inter-patient variation.

Suitably the buffer is capable of generating a pH in the range 3.5 to 6 in a 1% aqueous solution, preferably a pH in the range 4 to 4.5, particularly in the range 4 to 4.2

Suitably the dosage forms of this invention comprise a pharmaceutically acceptable addition salt of cimetidine.

Preferably the dosage form of this invention comprises a pharmaceutically acceptable acid addition salt of cimetidine and a buffer that is capable of generating a pH in the range 4.0 - 4.2 in a 1% aqueous solution, coated with a release delaying substance which does not permit more than 10% release of cimetidine after 2 hours in 0.1 N hydrochloric acid and which satisfies each of the following dissolution tests (b) and (c) in a European Pharmacopoeia apparatus, with rotating paddle, 100 revolutions per minute at 37°C with 800 ml of buffered aqueous medium comprising sodium hydroxide and 0.04 moles of monopotassium phosphate :—

	T	Conditions	% Release of Cimetidine
5	E	After 2 hours in 0.1 N hydrochloric acid and a further time in dissolution medium at pH 6.0 or 6.8	Formulae with a pharmaceutically acceptable acid addition salt of cimetidine and a buffer.
10	T		
15	(b)	6.0	Minimum 60% after 2 hours
20	(c)	6.8	Minimum 90% after 1 hour

The particular dosage forms of the present invention can be any of the commonly used types of solid dosage form. Thus, for example, they can be coated tablets, capsules or granules.

Examples of buffers that can be used in this invention include those formed from citric, tartaric, benzoic and sorbic acids, alkali metal salts thereof, alkali metal phosphates and mixtures thereof. A suitable buffer comprises a mixture of monosodium citrate and disodium citrate.

Suitably the amount of buffer relative to cimetidine should be as much as possible to aid dissolution of cimetidine in the intestine. For a tablet or capsule the maximum amount will be dictated by the size of the unit dosage form which must not be too large to hinder oral administration. Suitably the amount of buffer is between 0.01 to 5 moles per mole of cimetidine, preferably between 0.1 to 0.5 moles per mole of cimetidine.

Examples of acid addition salts of cimetidine include those formed with hydrochloric, hydrobromic, sulphuric, phosphoric, acetic, citric, maleic, lactic, ascorbic, fumaric, oxalic, methanesulphonic and ethane sulphonic acids. Cimetidine hydrochloride is preferred.

In addition to cimetidine or a pharmaceutically acceptable acid addition salt and optionally a buffer, the delayed-release dosage form suitably comprises a pharmaceutically acceptable carrier formulation. Examples of excipients for such carriers include starch, celluloses, lactose, sucrose, magnesium stearate, polyvinylpyrrolidone and sodium laurylsulphate.

Suitably the release-delaying substance comprises a coating agent selected from methacrylic acid copolymers, polymeric methacrylates such as Eudragit® L, E, S, RL, RS, L 30 D, NE 30 D, RL 30 D, RS 30 D or mixtures thereof, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, ethyl cellulose or polyvinyl acetate phthalate, or mixtures thereof.

As well as the above-noted coating agents the release-delaying substance suitably comprises other coating additives well known in the coating art such as :

- plasticisers, e.g. acetylated monoglycerides, diethyl phthalate, triacetin, citric esters such as triethyl citrate, acetyl triethyl citrate, tributylcitrate or acetyl tributyl citrate, propylene glycol, tributyrine, butylphthalylbutyl glycolate, glycerine, polyethylene glycols, glyceryl triacetate, dibutyl sebacate, dibutyl phthalate, castor oil or acetyl monoglyceride,
- lubricants, e.g. calcium stearate, colloidal silicon dioxide, mineral oil, magnesium stearate, polyethylene glycol or talc ;
- stabilizers and emulsifying agents, e.g. calcium stearate, glyceryl monostearate, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polysorbate, propylene glycol, carboxymethyl-cellulose, dextrin, cetostearyl alcohol, mineral oil and lanolin alcohols, polyoxyethylene allyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene stearate or sorbitan esters,
- film disintegrating agents, e.g. lactose, saccharose, starch, cellulose, kaolin, polyvinyl alcohol or hydroxypropyl methyl cellulose ; or

- colouring agents.

The particular amounts of coating agent and coating additives used for the release-delays substance are variable within limits that can be determined by a skilled worker using the in vitro dissolution tests as hereinbefore defined.

5 Suitably the release-delays substance comprises :

	<u>% (w)</u>
10	Coating agent                          40 to 100
	Plasticiser                            0 to 20
	Lubricant                             0 to 40
	Film disintegrating agent        0 to 40

15 Preferably the coating agent used is Eudragit® L 30 D. Alternatively, a mixture of Eudragit® L 30 D and up to 25% of Eudragit® NE 30 D is used.

Eudragit® L 30 D is an aqueous dispersion containing 30% (w/w) of an acrylic resin formed from a copolymer based on polymethacrylic acid and acrylic acid esters. The acrylic resin is soluble in intestinal juice from pH 20 5.5 upwards.

Eudragit® NE 30 D is an aqueous dispersion containing 30% (w/w) of a neutral copolymer based on ethyl acrylate and methyl methacrylate.

A preferred plasticiser is triethyl citrate and a preferred lubricant is talc.

When the coating agent used comprises a mixture of Eudragit® NE 30 D and Eudragit® L 30 D preferably 25 an emulsifying agent such as polysorbate is also present.

When Eudragit® L 30 D is used as the coating agent, suitably the release-delays substance is present in an amount of approximately 2 to 30% (w/w) relative to the uncoated dosage form, preferably 2 to 14% (w/w).

In another aspect the present Invention provides a delayed-release oral dosage form comprising cimetidine or a pharmaceutically acceptable acid addition salt thereof and optionally a buffer that is capable of generating 30 a pH in the range 3.5 to 6 in a 1% aqueous solution, coated with a release-delays substance in an amount of 2 to 30% (w/w) relative to the uncoated dosage form, the release-delays substance comprising :

	<u>% (w)</u>
35	Coating agent                          40 to 100
	Plasticiser                            0 to 20
	Lubricant                             0 to 40
	Film disintegrating agent        0 to 40

40 For particulate dosage forms such as pellets or granules preferably the release-delays substance is present in an amount of 10 to 30% (w/w) relative to the uncoated dosage form. For larger dosage forms such as tablets preferably the release delaying substance is present in an amount of 2-20% (w/w) relative to the uncoated dosage form.

45 Examples of coating agents, plasticisers, lubricants and film disintegrating agents are as hereinbefore described. Particular examples of coating agents include Eudragit® L or L 30 D, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate or polyvinyl acetate phthalate or mixtures thereof.

A preferred coating agent is a copolymer of polymethacrylic acid and acrylic acid esters that is soluble in 50 intestinal juice from pH 5.5 upwards such as Eudragit® L 30 D.

Preferably the cimetidine is in the form of its hydrochloride.

Preferably the buffer is capable of generating a pH of 4 to 4.2 in a 1% aqueous solution.

Suitably the buffer comprises a mixture of monosodium citrate and disodium citrate.

In a further aspect of the invention, there is provided a multi-phase medicament comprising an immediate-release phase containing cimetidine or a pharmaceutically acceptable salt thereof, and at least one delayed-release phase comprising a composition as described above.

For example a suitable medicament can comprise an immediate-release phase to provide a first pulse of cimetidine, a first delayed-release phase to provide a second pulse of cimetidine and a second delayed release

phase having a greater amount of release delaying substance than the first delayed-release phase to provide a third pulse of cimetidine. In this manner the duration of action of cimetidine can be extended whilst maintaining good bioavailability. Alternatively the first delayed-release phase may contain a polymer which is soluble from pH 5.5 upwards (eg Eudragit® L 30 D) and the second delayed-release phase may contain a polymer which is soluble from pH 6 upwards (eg Eudragit® L). Due to the different solubilities of the polymers the first delayed-release phase will release cimetidine sooner than the second delayed phase in the intestinal tract.

5 The immediate and delayed-release phases can be presented separately or combined in a single dosage form. Thus, for example, a combination can take the form of a bilayer tablet or a layered tablet in which the immediate-release phase is compressed or coated around a delayed-release core. Alternatively, the immediate-release and delayed-release phases can take the form of uncoated and coated tablets or pellets contained within a gelatin capsule.

10 The immediate-release phase typically will comprise uncoated cimetidine, or cimetidine particles which are coated by a coating agent which dissolves in the gastric juices. Preferably the cimetidine is in the form of an acid addition salt as hereinbefore described. Preferably the immediate-release phase comprises a disintegrating agent such as starch, cellulose, sodium croscarmellose, sodium starch glycolate, crospovidone, kaolin, polyvinyl alcohol or low viscosity hydroxypropyl methyl celluloses.

15 Suitably the delayed-release cimetidine and the immediate-release cimetidine are administered in a ratio 5 : 1 to 1 : 1, suitably 3 : 1 to 1 : 1, preferably in a ratio of 5 : 3, calculated as the free base of cimetidine. Thus, for a single 800 mg dose of cimetidine it is possible to administer 2 delayed-release cimetidine tablets (each containing 250 mg of cimetidine hydrochloride calculated as the free base) and 2 immediate-release cimetidine tablets (each containing 150 mg of cimetidine hydrochloride calculated as the free base). More conveniently a single dosage form comprises 250 mg of delayed-release cimetidine hydrochloride surrounded by 150 mg of immediate-release cimetidine hydrochloride, both calculated as the free base. Other embodiments include a capsule containing a tablet of immediate-release cimetidine (300 mg) and a tablet of delayed-release cimetidine (300 mg) or a capsule containing uncoated pellets of cimetidine (60 mg) and coated pellets of cimetidine (240 mg).

20 In another aspect of the invention, there is provided a medicament comprising a delayed-release phase containing cimetidine as hereinbefore defined and a further therapeutic agent which is in a form which enables it to be released in the stomach.

25 The further therapeutic agent can be, for example, an antacid such as magnesium hydroxide or an alkali metal or alkaline earth metal carbonate or bicarbonate or a stomach mucosa protective agent such as sucralfate.

30 The cimetidine phase and the phase containing the other therapeutic agent can be presented as separate entities or combined in a single dosage form in a manner analogous to that described above for the immediate-release delayed-release multi-phase cimetidine medicaments.

35 In a preferred embodiment, the medicament comprises a sucralfate layer compressed around a cimetidine-containing coated core.

The invention will now be illustrated by means of the following description, bioavailability study results and examples.

#### 40 Description - In Vitro Dissolution Tests

##### Apparatus

45 All parts of the apparatus which come into contact with the sample or with the dissolving medium must be chemically inert and must neither adsorb the substance to be examined nor react in its presence, nor affect its behaviour.

No part of the apparatus nor the assembly in which it is situated should exert any significant movement of stirring or of vibration other than those of the low-speed rotating element.

50 The dissolution apparatus, called a paddle apparatus, consists of a cylindrical vessel, a stirrer and a thermostated bath.

The hemispherical-bottomed cylindrical vessel, of nominal capacity 1000 ml, is made of borosilicate glass or another appropriate transparent material. The vessel is fitted with a lid to prevent evaporation and having a central aperture for the stirrer shaft and also several other apertures allowing a thermometer and sampling devices to be introduced.

55 The stirrer consists of a vertical shaft to the lower part of which is attached a paddle whose shape corresponds to that of the portion of a circle bounded by two parallel planes. The paddle is inserted into the centre of the shaft in such a way that its base is at exactly the level of the end of the shaft. The shaft is positioned so

that its axis is not more than 2 mm from that of the vessel and the lower part of the paddle is situated at a distance of  $25 \pm 2$  mm from the bottom of the vessel. The upper part of the shaft of the stirrer is connected to a motor equipped with a speed regulator. The rotation of the stirrer must be uniform, without significant oscillation.

The thermostatted bath in which the vessel is immersed must allow the temperature of the solution medium to be maintained at  $37 \pm 0.5^\circ\text{C}$  during the test.

### Reagents

- 0.1 N Hydrochloric acid
- 10 — pH 5.7 buffer :  
To 250 ml of 0.2 M monopotassium phosphate solution (27.22 g of  $\text{KH}_2\text{PO}_4$  per litre) add 735 ml of purified water, adjust the pH to  $5.7 \pm 0.05$  by means of a 0.2 N solution of sodium hydroxide (about 20 ml). Make up to 1000 ml with purified water. Mix.
- 15 — pH 6.0 buffer :  
To 250 ml of 0.2 M monopotassium phosphate solution (27.22 g of  $\text{KH}_2\text{PO}_4$  per litre) add 715 ml of purified water, adjust the pH to  $6 \pm 0.05$  by means of a 0.2 N solution of sodium hydroxide (about 31 ml). Make up to 1000 ml with purified water. Mix.
- 20 — pH 6.8 buffer :  
To 250 ml of 0.2 M monopotassium phosphate solution (27.22 g of  $\text{KH}_2\text{PO}_4$  per litre) add 620 ml of purified water, adjust the pH to  $6.8 \pm 0.05$  by means of a 0.2 N solution of sodium hydroxide (about 125 ml). Make up to 1000 ml with purified water. Mix.

### Procedure

- 25 — Standard solution  
Introduce an exactly weighed test amount  $P_s$  of about 79 mg of standard reference cimetidine into a 500 ml volumetric flask. Dissolve and make up to 500 ml with the buffer under study (buffer of pH 5.7, 6.0 or 6.8). Mix.  
Dilute this solution to exactly one 5 th with 0.1 N hydrochloric acid.
- 30 — Operating procedure  
Introduce 800 ml of the dissolving medium into the vessel. Assemble the apparatus. Warm the dissolving medium to  $37 \pm 0.5^\circ\text{C}$  and withdraw the thermometer.  
Place the product at the bottom of the vessel before the paddle is set in motion.  
When placing the product under study in the apparatus, take care to avoid the formation of bubbles on the surface of the sample and immediately set the apparatus in motion at the speed of 100 RPM, controlled to a precision of  $\pm 4$  percent. Every 15 minutes, take a sample (5 ml) in a region halfway between the surface of the liquid and the top of the paddle and at least 10 mm from the wall of the vessel.  
Compensate the amount removed for calculations.  
Filter the samples at  $37^\circ\text{C}$  and carry out a dilution to one 5 th in 0.1 N hydrochloric acid.
- 40 Read the absorbance of each dilution in a 1 cm cuvette at 218 nm and at 260 nm, taking a dilution of the buffer studied to one 5 th in 0.1 N hydrochloric acid as the compensation liquid.  
Read the absorbance of the standard solution under the same conditions.  
For the standard solution and each dilution prepared from each of the samplings, calculate :  
$$\Delta(\text{OD}) = \text{OD}_{218 \text{ nm}} - \text{OD}_{260 \text{ nm}}$$
- 45 From the  $\Delta(\text{OD})$  value found for the standard solution, the value  $P_s$  and the  $\Delta(\text{OD})$  values obtained for each sampling, calculate the percentage of the active principle dissolved at each time, allowing for the quantities sampled for the measurement.

### Results

50 The tablets of Examples 1 and 2 gave 0% dissolution after 2 hours in 0.1 N hydrochloric acid and satisfied each of the tests (a) to (c) as follows :

		Conditions	% Release of Cimetidine	
			Formulae with Cimetidine base	
			Example 1	Example 2
5	T	After 2 hours in 0.1 N hydro- chloric acid and a further time in dissolution medium at pH 5.7, 6.0 or 6.8		
10	E			
15	S			
20	T			
25	(a)	5.7	100 after 2 hours	100 after 2 hours
30	(b)	6.0	91 after 1 hour	100 after 1 hour
	(c)	6.8	95 after 45 mins.	100 after 45 mins.

The tablets of Examples 3 to 6 gave 0% dissolution after 2 hours in 0.1 N hydrochloric acid and satisfied each of the tests (b) and (c) as follows :

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Conditions		% Release of Cimetidine			
T	E S T	Formulae with Cimetidine Hydrochloride			
		Ex 3	Ex 4	Ex 5	Ex 6
(b)	6.0	100 after 2 hrs	100 after 2 hrs	95.5 after 2 hrs	100 after 2 hrs
(c)	6.8	100 after 45 mins.	100 after 45 mins.	99.5 after 45 mins.	91.4 after 45 mins.

The tablets of Examples 7 to 9 gave 0% release of cimetidine after 2 hours in 0.1 N hydrochloric acid and satisfied each of the tests (b) and (c) as follows :

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		Conditions	% Release of Cimetidine		
			Formulae with Cimetidine Hydrochloride & buffer		
T	E	After 2 hours in 0.1 N hydro-chloric acid and a further time in dissolution medium at pH 6.0 or 6.8	Ex 7	Ex 8	Ex 9
(b)	6.0	100 after 2 hours	66.8 after 2 hours	81.0 after 2 hours	
(c)	6.8	100 after 1 hour	100 after 1 hour	97.1 after 1 hour	

Bioavailability study results

The following treatments were used to assess the bioavailability of the formulations of the present invention:

Treatment A' : Two 110 mg tablets of Example 1  
 Treatment B' : Two 110 mg tablets of Example 2  
 Treatment C' : Two 110 mg tablets of Example 3  
 Treatment D' : One 200 mg Tagamet<sup>R</sup> tablet (immediate-release).

Treatment A : Two 250 mg tablets of Example 4 + two 150 mg tablets of Example 10.

Treatment B : Two 250 mg tablets of Example 8 + two  
                   150 mg tablets of Example 10.

5           Treatment C : Two 250 mg tablets of Example 7 + two  
                   150 mg tablets of Example 10.

Treatment D : Two 250 mg tablets of Example 6 + two  
                   150 mg tablets of Example 10.

10          Treatment E : Two 250 mg tablets of Example 5 + two  
                   150 mg tablets of Example 10.

Treatment F : Two 250 mg tablets of Example 9 + two  
                   150 mg tablets of Example 10.

15          Treatment G : One 800 mg Tagamet<sup>R</sup> tablet  
                   (immediate-release).

20          A first group of three patients each received a 220 mg dose of cimetidine according to treatments A', B'  
                   and C'. One patient within this group also received subsequently a 200 mg dose of cimetidine according to treat-  
                   ment D'.

25          A second group of three patients each received an 800 mg dose of cimetidine according to treatments A,  
                   C, E and G. A third group of three patients each received an 800 mg dose of cimetidine according to treatments  
                   B, D, F and G. At least seven days elapsed between each treatment. Blood plasma levels were monitored from  
                   which the following parameters were determined :

30          T<sub>max</sub> (hours)   : Time to reach maximum plasma  
                           concentration

35          C<sub>max</sub> (mg/l)   : Maximum plasma concentration

T<sub>0.5</sub> (hours)   : Time during which plasma concentration  
                           is greater than 0.5 mg/l

AUC (mg/h/l)   : Area under plasma concentration against  
                           time curve.

40          The following results were obtained :

45           Group 1

45       Treatment	A'	B'	C'	D'
50       T <sub>max</sub>	3.66	3.02	2.28	0.75
C <sub>max</sub>	0.71	0.86	1.25	1.06
T <sub>0.5</sub>	1.86	1.90	2.23	1.50
AUC	2.86	2.93	3.30	2.64

## Group 2

Treatment	A	C	E	G
T <sub>max</sub>	3.44 (0.42)	4.55 (0.63)	3.58 (0.58)	1.75 (0.74)
C <sub>max</sub>	4.71 (0.74)	3.27 (0.26)	4.12 (0.55)	3.83 (0.81)
T <sub>0.5</sub>	8.48 (0.22)	8.93 (0.16)	8.31 (1.00)	6.74 (0.89)
AUC	17.06 (2.35)	14.36 (0.39)	15.33 (1.65)	14.17 (1.63)

## Group 3

Treatment	B	D	F	G
T <sub>max</sub>	5.00 (0.00)	4.50 (0.41)	4.33 (0.94)	1.33 (0.31)
C <sub>max</sub>	3.05 (1.12)	3.18 (0.54)	3.24 (1.15)	4.81 (0.90)
T <sub>0.5</sub>	9.17 (1.11)	9.21 (0.08)	9.81 (1.09)	8.09 (0.67)
AUC	14.76 (4.02)	14.61 (1.47)	15.38 (3.15)	17.51 (1.82)

Figures in parenthesis represent standard deviations.

A direct comparison of the results in Group 1 cannot be made since treatments A', B' and C' used 10% more cimetidine than treatment D'. However, it is still evident that the tablets of Examples 1 to 3 exhibit delayed-release characteristics (T<sub>max</sub> has been extended) whilst maintaining adequate bioavailability (as demonstrated by T<sub>0.5</sub> and AUC).

Comparing the results of treatments A, C, E and G in group 2 it is evident that treatment using compositions of the present invention prolong the duration of action by about 1.6 to 2.2 hours (as measured by T<sub>0.5</sub>) and increase the bioavailability (as measured by AUC). Although results in Group 3 indicates that the bioavailability following treatment B, D or F is less than that following treatment G, the time during which plasma concentrations are greater than the therapeutically effective level of 0.5 mg/l is extended by more than one hour.

#### Example 1

##### 50 Delayed-release (Cimetidine free base/ Eudragit L 30 D and NE 30 D Coating)

<u>Ingredients</u>	<u>mg./tablet</u>
Cimetidine	110.000
Corn Starch	3.685
Microcrystalline cellulose	0.887
Sodium starch glycolate	4.443
Polyvinylpyrrolidone	3.685
Sodium laurylsulphate	0.275
Magnesium stearate	0.670

Half of the polyvinylpyrrolidone was dissolved in purified water to give a 9% w/v solution. The sodium laurylsulphate was dissolved in this solution. The cimetidine, starch and the remainder of the polyvinylpyrrolidone were introduced into a fluidised bed granulator and granulated with the above solution. The wet granulation was dried, to give a residual moisture content of 2.2% (w/w), and then screened through a 1.2 mm mesh screen. The remaining excipients were added and mixed and the mixture was compressed into a tablet core.

The tablet cores were each coated with a coating suspension having the following composition :

<u>Ingredients</u>	<u>% w/w</u>
Eudragit N E 30 D	6.67
Eudragit L 30 D	20.00
Polysorbate 80	0.40
Talc	4.00
Triethyl citrate	0.90
Purified Water	68.03

The tablet cores were coated using a Uniglatt fluidised bed apparatus fitted with a six inch Wurster bottom spray apparatus. The operating conditions were as follows :

Charge	400 g. of tablets
Temperature at the entry	60 - 65°C.
Air intake valve	Position 30
Pipe	1 mm
Spraying pressure	2.1 - 2.2 bars
Core pre-heating	air outlet 34° C.
Flow	8.6 g/minute
Amount of coating suspension sprayed	500 g
Air outlet temperature during process	34-36° C.

At the end of the operation, the tablets were dried in an open air oven for one night.

	Quantity of coated tablets recovered	: 440.6g
5	Average weight of coated tablet	: 136.09mg
	Average weight of tablet core	: 123.26mg
	Approximate weight of tablet coating	: 12.83mg
10	Average thickness of coated tablet	: 4.52mm
	Average thickness of tablet core	: 4.29mm
	Approximate thickness of tablet coating	: 0.115mm.
	* weight of coating relative to tablet core :	10.4

15 Example 2Delayed-release (Cimetidine free base/Eudragit L 30 D Coating)

Tablet cores as prepared in Example 1 were each coated with a coating suspension having the following composition :

	<u>Ingredients</u>	<u>g (w/w)</u>
25	Eudragit L 30 D	26.64
	Talc	4.00
	Triethylcitrate	1.20
	Purified Water	68.16

30 The coating procedure and coating conditions were substantially as described in Example 1 except that, for 400 g of tablet cores, 400.4 g of coating suspension was used.

35	Average weight of coated tablet	: 136.01mg
	Average weight of tablet core	: 123.27mg
	Approximate weight of tablet coating	: 12.74mg
40	Average thickness of coated tablet	: 4.58mm
	Average thickness of tablet core	: 4.40mm
	Approximate thickness of tablet coating	: 0.09mm.
	* weight of coating relative to tablet core :	10.3

45 Example 3Delayed-release(Cimetidine HC1/Eudragit L 30 D Coating)

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55

	<u>Ingredients</u>	<u>mg./tablet</u>
5	Cimetidine base in the form of its hydrochloride	110.000*
	Corn Starch	3.685
	Microcrystalline cellulose	0.887
10	Sodium starch glycolate	4.443
	Polyvinylpyrrolidone	3.685
	Sodium laurylsulphate	0.275
	Magnesium stearate	0.670

15

\* corresponding to 133.76 mg of cimetidine hydrochloride monohydrate.

Half of the polyvinylpyrrolidone was dissolved in purified water to give a 9% w/v solution. The sodium laurylsulphate was dissolved in this solution. The cimetidine, starch and the remainder of the polyvinylpyrrolidone were mixed, moistened with the above solution and, if necessary, with further purified water and then granulated through a 3.15 mm mesh grid. The wet granulation was dried in a fluidised bed dryer, to give a residual moisture content of 5.0% (w/w), and then screened through a 1.25 mm mesh screen. The remaining excipients were added and mixed and the mixture was compressed into a tablet core.

The tablet cores were each coated with a coating suspension having the same composition as described in Example 2.

25 The coating procedure and coating conditions were substantially as described in Example 1, except that, for 400 g of tablet cores, 250.25 g of coating suspension was used.

Average weight of coated tablet	: 154.78mg
30 Average weight of tablet core	: 146.67mg
Approximate weight of tablet coating	: 8.11mg
Average thickness of coated tablet	: 4.42mm
35 Average thickness of tablet core	: 4.29mm
Approximate thickness of tablet coating	: 0.065mm.
40 % weight of coating relative to tablet core :	5.5

#### Example 4

##### Delayed-release(Cimetidine HC1/Eudragit L 30 D Coating)

	<u>Ingredients</u>	<u>mg./tablet</u>
45	Cimetidine base in the form of its hydrochloride	250.000*
	Corn Starch	8.374
50	Microcrystalline cellulose	2.016
	Sodium starch glycolate	10.101
	Polyvinylpyrrolidone	8.374
55	Sodium laurylsulphate	0.624
	Magnesium stearate	2.380

\* corresponding to 304 mg of cimetidine hydrochloride monohydrate.

Half of the polyvinylpyrrolidone was dissolved in purified water to give a 9% w/v solution. The sodium lauryl sulphate was dissolved in this solution. The cimetidine, starch and the remainder of the polyvinylpyrrolidone were mixed, moistened with the above solution and, if necessary, with further purified water and then granulated through a 2.5 mm mesh grid. The wet granulation was dried in a fluidised bed dryer, to give a residual moisture content of 5.6% (w/w), and then screened through a 1 mm mesh screen. The remaining excipients were added and mixed and the mixture was compressed into a tablet core.

5 The tablet cores were each coated with a coating suspension having the same composition as described in Example 2.

10 The tablet cores were coated using a Erweka coating turbine, a Master drying gun and a Uniglatt coating gun. The operating conditions for 400 g of tablet cores are as follows :

Pre-heating

15	turbine speed	: 5 revs/min.
	air temperature	: 60°C
	temperature of tablets	: 32°C
20	pre-heating time	: 5 minutes.

Coating

25	distance from nozzle to tablet bed	: 13 cm
	flow	: 7 g/min
	spraying pressure	: 0.5 bars
	turbine speed	: 16 revs/min.
30	air temperature	: 60°C
	temperature of tablets	: 26-28°C
	process time	: 65 minutes

35	quantity of coating suspension sprayed	: 413 g
----	---	---------

40	Average weight of coated tablet	: 350.75mg
	Average weight of tablet core	: 336.20mg
	Approximate weight of tablet coating	: 14.55mg
45	Average thickness of coated tablet	: 5.22mm
	Average thickness of tablet core	: 5.13mm
	Approximate thickness of tablet coating	: 0.045mm
	* weight of coating relative to tablet core	: 4.32.

50

Example 5

Delayed-release (Cimetidine HC1/Eudragit L 30 D Coating)

55 Tablet cores as prepared in Example 4 were each coated with a coating suspension having the same composition as described in Example 2. The coating procedure and coating conditions were substantially as described in Example 4 except that, for 500 g of tablet cores, 1001 g of coating suspension was used.

	Average weight of coated tablet	: 374.10mg
	Average weight of tablet core	: 336.20mg
5	Approximate weight of tablet coating	: 37.90mg
	Average thickness of coated tablet	: 5.34mm
	Average thickness of tablet core	: 5.13mm
10	Approximate thickness of tablet coating	: 0.105mm.
	% weight of coating relative to tablet core :	11.3.

Example 615 Delayed-release (Cimetidine HC1/Eudragit L 30 D and NE 30 D Coating)

Tablet cores as prepared in Example 4 were each coated with a coating suspension having the same composition as described in Example 1.

The coating procedure and coating conditions were substantially as described in Example 4, except that 20 for 500 g of tablet cores, 937.7 g of coating suspension was used.

	Average weight of coated tablet	: 368.55mg
	Average weight of tablet core	: 336.20mg
25	Approximate weight of tablet coating	: 32.35mg
	Average thickness of coated tablet	: 5.30mm
	Average thickness of tablet core	: 5.13mm
30	Approximate thickness of tablet coating	: 0.085mm.
	% weight of coating relative to tablet core :	9.6.

Example 735 Delayed-release (Cimetidine HC1+ Citrate buffer/Eudragit L 30 D Coating)

	<u>Ingredients</u>	<u>mg./tablet</u>
40	Cimetidine base in the form of its hydrochloride	250.000*
	Corn Starch	8.374
45	Microcrystalline cellulose	2.016
	Sodium starch glycolate	10.101
	Polyvinylpyrrolidone	8.374
	Sodium laurylsulphate	0.624
50	Magnesium stearate	2.380
	Monosodium citrate	56.958
	Disodium citrate 1.5 H <sub>2</sub> O	27.760

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\* corresponding to 304 mg of cimetidine hydrochloride monohydrate.

Half of the polyvinylpyrrolidone was dissolved in purified water to give a 9% w/v solution. The sodium lauryl-sulphate was dissolved in this solution. The cimetidine, starch, monosodium and disodium citrates and the

remainder of the polyvinylpyrrolidone were mixed, moistened with the above solution and, if necessary, with further purified water and then granulated through a 2.5 mm mesh grid. The wet granulation was dried in a fluidised bed dryer, to give a residual moisture content of 5.3% (w/w), and then screened through a 1 mm mesh screen. The remaining excipients were added and mixed and the mixture was compressed into a tablet core.

5 The tablet cores were each coated with a coating suspension having the same composition as described in Example 2. The coating procedure and coating conditions were substantially as described in Example 4 except that, for 500 g of tablet cores, 750.79 g of coating suspension was used.

10	Average weight of coated tablet	:	454.10mg
	Average weight of tablet core	:	423.70mg
	Approximate weight of tablet coating	:	31.40mg
15	Average thickness of coated tablet	:	5.54mm
	Average thickness of tablet core	:	5.39mm
	Approximate thickness of tablet coating	:	0.075mm.
	% weight of coating relative to tablet core :		7.4.

20 Example 8

Delayed-release (Cimetidine HC1+ citrate buffer/Eudragit L 30 D Coating)

25 Tablet cores as prepared in Example 7 were each coated with a coating suspension having the same composition as described in Example 2. The coating procedure and coating conditions were substantially as described in Example 4 except that, for 500 g of tablet cores, 1001 g of coating suspension was used.

30	Average weight of coated tablet	:	467.60mg
	Average weight of tablet core	:	422.70mg
	Approximate weight of tablet coating	:	44.90mg
35	Average thickness of coated tablet	:	5.60mm
	Average thickness of tablet core	:	5.39mm
	Approximate thickness of tablet coating	:	0.105mm.
	% weight of coating relative to tablet core :		10.6.

40 Example 9

Delayed-release (Cimetidine HC1+Citrate Buffer/Eudragit L 30 D and NE 30 D Coating)

45 Tablet cores as prepared in Example 7 were each coated with a coating suspension having the same composition as described in Example 1. The coating procedure and coating conditions were substantially as described in Example 4 except that, for 500 g of tablet cores, 937.7 g of Eudragit coating suspension was used.

Average weight of coated tablet	: 479.40mg
Average weight of tablet core	: 422.70mg
Approximate weight of tablet coating	: 56.70mg
Average thickness of coated tablet	: 5.66mm
Average thickness of tablet core	: 5.39mm
Approximate thickness of tablet coating	: 0.135mm.
t weight of coating relative to tablet core :	13.4.

Example 1015 Immediate-release phase (Cimetidine hydrochloride)

	<u>Ingredients</u>	<u>mg./tablet</u>
20	Cimetidine base in the form of its hydrochloride	150.000*
	Corn Starch	9.000
25	Microcrystalline cellulose	98.000
	Sodium starch glycolate	12.000
	Polyvinylpyrrolidone	9.000
30	Sodium laurylsulphate	0.600
	Magnesium stearate	3.144
	Lactose (fast flow)	35.714
	Lactose (Codex)	99.286

35 \* corresponding to 182.4 mg of cimetidine hydrochloride monohydrate.

Half of the polyvinylpyrrolidone was dissolved in purified water to give a 9% w/v solution. The sodium laurylsulphate was dissolved in this solution. The cimetidine, starch, lactose and the remainder of the polyvinylpyrrolidone were mixed, moistened with the above solution and, if necessary, with further purified water and then granulated through a 2.5 mm mesh grid. The wet granulation was dried in a fluidised bed dryer, to give a residual moisture content of 3.0% (w/w), and then screened through a 1.25 mm mesh screen. The remaining excipients were added and mixed and the mixture was compressed into a tablet core.

Example 1145 Delayed-release/Immediate-release tablets

An immediate-release phase of cimetidine hydrochloride was prepared as described in Example 10 and was compressed around the delayed-release phase tablets prepared as in Example 7. Tablets comprising 250 mg of delayed-release cimetidine (in the form of its hydrochloride) and 150 mg of immediate-release cimetidine (in the form of its hydrochloride) were thereby obtained.

Example 12Delayed-release/Immediate-release tablets

55 Delayed-release tablets as prepared in Example 7 were each coated with a coating solution having the following composition:

	% (w/w)	
5	Cimetidine hydrochloride	15.796
	Hydroxypropyl methylcellulose 15 cp	1.380
	Hydroxypropyl methylcellulose 5 cp	3.220
10	Propylene glycol	0.460
	Purified Water	79.144

Tablets were coated using a Erweka coating turbine, a master drying gun and a Uniglitz coating gun. The operating conditions for 500 g of tablets are as follows :

15           Pre-heating

turbine speed	:	5 revs/min
air temperature	:	75°C
temperature of tablets	:	38°C
20           pre-heating time	:	5 min.

25           Coating

distance from nozzle to tablet bed	:	12 cm
flow	:	4 g/min
spraying pressure	:	0.7 bar
30           turbine speed	:	16 revs/min
air temperature	:	75°C
temperature of tablets	:	38°C
35           process time	:	5 h 10 min
quantity of coating solution sprayed	:	1232 g
40           Average weight of tablets before spraying	:	
	:	454.10 mg
45           Average weight of tablets after spraying with immediate-release phase	:	682 mg
Approximate weight of immediate-release coating	:	227.9 mg.

50           The above coating conditions result in tablets wherein the immediate-release phase has the following composition :

	<u>mg/tablet</u>
5	Cimetidine base in the form of its hydrochloride
	150.000*
10	Hydroxypropyl methylcellulose 15 cp
	15.000
15	Hydroxypropyl methylcellulose 5 cp
	35.000
	Propylene glycol
	5.000

\* corresponding to 171.675 mg of anhydrous cimetidine hydrochloride.

#### Example 13

##### Cimetidine/Sucralfate Tablet

This is prepared by compressing a sucralfate immediate-release phase around the delayed-release cimetidine tablets of Example 7.

##### Sucralfate Immediate-Release Phase

	<u>Ingredients</u>	<u>Mg./Tablet</u>
25	Sucralfate	500.00
	Polyethyleneglycol 6000	15.16
	Corn Starch	90.80
	Magnesium Stearate	<u>3.04</u>
30		<b>609.00</b>

The polyethyleneglycol 6000 is dissolved in sufficient distilled water to make a 3.5% (w/w) solution. The starch and sucralfate are mixed and granulated with the polyethyleneglycol solution. The granulation is screened (2.5 mm mesh screen) and dried. Magnesium stearate is mixed with the dried granules.

35 The above immediate-release granules are then press-coated around the delayed-release core using a multilayer rotary tablet machine, to give delayed-release cimetidine/immediate-release sucralfate tablets.

Instead of preparing a single cimetidine/sucralfate tablet, the same dose may be provided by two tablets prepared in analogous manner but each containing half the ingredients of the single dosage form.

#### Example 14

##### Repeat Action Capsules (Cimetidine Free Base/Eudragit L 30 D Coating)

One immediate-release (core) and one delayed release (enteric coated) tablet are contained within a hard gelatin capsule.

	<u>Core Manufacture</u>	
	<u>Ingredients</u>	<u>mg/Tablet</u>
5	Cimetidine	300.00
	Corn Starch	15.00
	Microcrystalline Cellulose	5.00
10	Sodium Starch Glycollate	12.00
	Polyvinylpyrrolidone	12.00
	Magnesium Stearate	<u>3.00</u>
15		<u>347.00</u>

The cimetidine, starch, and polyvinylpyrrolidone are introduced into a Pharma Melt® high speed blender/granulator. The powders are mixed together before they are granulated with purified water. The wet granulation is dispensed onto trays and dried in an oven at 60°C to give a target residual moisture content of 0.8% w/w, within the limits of 0.6-1.0% w/w. The dry granules are then screened through a 12 mesh sieve and blended with the remaining excipients using the cone blender. The mixture is then compressed into 7.5 mm diameter tablet cores with a theoretical weight of 347.0 mg ± 3%, having an average hardness of 16.1 SC.

25 Coating  
 Tablets intended to give delayed-release are coated with a coating suspension having the following composition :

30	<u>Ingredients</u>	<u>% w/v</u>
	Eudragit L30D	53.3
35	Talc	1.6
	Polyethylene Glycol	1.6
	Antifoam Emulsion	0.1
	Purified Water	43.4

40 The tablet cores are coated using a twenty-four inch round backed, stainless steel coating pan fitted with a Manesty spray gun and Spraytab unit. The operating conditions are as follows :

45	Inlet air temperature	60°C (approx)
	Spray Nozzle details	1.5 mm needle with 1.8-2.0 mm nozzle
	Pan Speed	12 rpm
50	Spraying Pressure	50 psi
	Tablet bed temperature	30-33°C
	Process Time	180 minutes

Average weight of coated tablets	384.3 mg
Average weight of tablet cores	345.4 mg
Approximate weight of tablet coat	38.9 mg
% Weight of coat (relative to tablet core)	11.26

Encapsulation

The tablets are encapsulated using a capsule filling machine. The empty gelatin capsules are separated by the machine and using an attached tablet counter-feeder, are filled with one tablet core and one coated tablet. The capsule contents are checked prior to closure.

To keep the dosage size to a minimum, an optimum capsule size and shape is used, eg Capsugel's Coni-snap Supro® Size A.

15

Example 15Repeat Action Capsules (Cimetidine Free Base/Eudragit L 30 D Coating)

Uncoated immediate-release cimetidine pellets and enterically-coated cimetidine pellets are contained within a hard gelatin capsule.

Manufacture of Uncoated Pellets

25

	<u>Ingredients</u>	<u>% w/w</u>
	Cimetidine	85
30	Microcrystalline Cellulose	12
	Gelatin	3
	(Water	qs)

35

The cimetidine and part of the microcrystalline cellulose are dry blended in a high shear mixer. Mixing is continued while a solution of the gelatin in water is added. When homogeneously massed the material is passed through an extruder and recirculated through it once. The extrudate is transferred to a Marumerizer bowl and spheronized. The rest of the microcrystalline cellulose is used as dusting powder to facilitate this stage of the process. The pellets are discharged and spread out on trays to be dried in a hot air oven. The dried pellets are screened between 1.4 mm and 0.6 mm to remove oversize and undersize fractions.

Coating of Pellets

45

	Composition of coating suspension	% w/w
	Eudragit L30D	51.2
50	Triethyl citrate	2.3
	Colloidal silicon dioxide	1.2
	Water	45.3

55

Pellets obtained as described above are coated by bottom spraying with the coating suspension in Fluidised Bed equipment until a 20% gain in weight is achieved. These coated pellets therefore contain  $85/120 = 70.8\%$  of cimetidine. The coated pellets are dried *in situ* before discharge, and then allowed to cure overnight at room temperature, while spread out on trays. The approximate weight of a coated pellet is about 0.8 mg.

Encapsulation

Uncoated and coated pellets are filled into capsules such that one capsule contains :  
 70.6 mg of uncoated pellets comprising 60 mg cimetidine  
 5 338.8 mg of coated pellets comprising 240 mg cimetidine  
 Thus two capsules provide a 600 mg dose of cimetidine wherein the ratio of delayed-release to immediate-release cimetidine is 4 : 1.  
 Eudragit is a registered trademark of Röhm Pharma GmbH, Weiterstadt, D-6100 Darmstadt 1, Germany.

10 **Claims**

15 1. A delayed-release oral dosage form comprising cimetidine or a pharmaceutically acceptable acid addition salt thereof, coated with a release-delaying substance which does not permit more than 10% release of cimetidine after 2 hours in 0.1 N hydrochloric acid and which satisfies each of the following dissolution tests (a) to (c) in a European Pharmacopoeia apparatus, with rotating paddle, 100 revolutions per minute, at 37°C with 800 ml of buffered aqueous dissolution medium comprising sodium hydroxide and 0.04 moles of monopotassium phosphate :—

		Conditions		% Release of Cimetidine	
T	E	S	T	Formulae with Cimetidine base	Formulae with a pharmaceutically acceptable acid addition salt of cimetidine.
	After 2 hours in 0.1 N hydro-chloric acid and a further time in dissolution medium at pH 5.7, 6.0 or 6.8				
(a)	5.7		Minimum 85% after 2 hours		Not applicable
(b)	6.0		Minimum 75% after 1 hour	Minimum 75% after 2 hours	
(c)	6.8		Minimum 90% after 45 mins.	Minimum 80% after 45 mins.	

50 2. A delayed-release oral dosage form comprising cimetidine or a pharmaceutically acceptable acid addition salt thereof and a buffer that is capable of aiding dissolution of cimetidine in the intestine, coated with a release-delaying substance which does not permit more than 10% release of cimetidine after 2 hours in 0.1 N hydrochloric acid and which satisfies each of the following dissolution tests (b) and (c) in a European Pharmacopoeia apparatus, with rotating paddle, 100 revolutions per minute, at 37°C with 800 ml of buffered aqueous dissolution medium comprising sodium hydroxide and 0.04 moles of monopotassium phosphate :—

		Conditions	% Release of Cimetidine
5	T E S T	After 2 hours in 0.1 N hydrochloric acid and a further time in dissolution medium at pH 6.0 or 6.8	Formulae with cimetidine or a pharmaceutically acceptable acid addition salt thereof and a buffer.
15	(b)	6.0	Minimum 50% after 2 hours
20	(c)	6.8	Minimum 85% after 1 hour

3. A dosage form according to claim 2 wherein the buffer is capable of generating a pH in the range 3.5 to 6 in a 1% aqueous solution.

25 4. A dosage form according to claim 2 or 3 which comprises a pharmaceutically acceptable acid addition salt of cimetidine and a buffer that is capable of generating a pH in the range 4.0 - 4.2 in a 1% aqueous solution, coated with a release-delaying substance which does not permit more than 10% release of cimetidine after 2 hours in 0.1 N hydrochloric acid and which satisfies each of the following dissolution tests (b) and (c) in a European Pharmacopoeia apparatus, with rotating paddle, 100 revolutions per minute at 37°C with 800 ml of buffered aqueous medium comprising sodium hydroxide and 0.04 moles of monopotassium phosphate :—

30

		Conditions	% Release of Cimetidine
35	T E S T	After 2 hours in 0.1 N hydrochloric acid and a further time in dissolution medium at pH 6.0 or 6.8	Formulae with a pharmaceutically acceptable acid addition salt of cimetidine and a buffer.
40	(b)	6.0	Minimum 60% after 2 hours
45	(c)	6.8	Minimum 90% after 1 hour

55 5. A dosage form according to any one of claims 2 to 4 wherein the buffer comprises citric, tartaric, benzoic or sorbic acids, alkali metal salts thereof, alkali metal phosphates or mixtures thereof.

6. A dosage form according to claim 5 wherein the buffer comprises a mixture of monosodium citrate and disodium citrate.

5 7. A dosage form according to any one of claims 2 to 6 wherein the amount of buffer is between 0.01 to 5 moles per mole of cimetidine.

8. A dosage form according to claim 7 wherein the amount of buffer is between 0.1 to 0.5 moles per mole of cimetidine.

10 9. A dosage form according to any one of claims 1 to 8 wherein the cimetidine is in the form of its hydrochloride.

10 10. A dosage form according to any one of claims 1 to 9 wherein the release-delaying substance comprises a coating agent selected from methacrylic acid copolymers, polymeric methacrylates such as Eudragit<sup>R</sup> L, E, S, RL, RS, L 30 D, NE 30 D, RL 30 D, RS 30 D or mixtures thereof, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, ethyl cellulose or polyvinyl acetate phthalate, or mixtures thereof.

15 11. A dosage form according to claim 10 where the release-delayed substance comprises:

	<u>% (w)</u>
20	Coating agent                          40 to 100.
	Plasticiser                            0 to 20
25	Lubricant                              0 to 40
	Film disintegrating agent            0 to 40

12. A dosage form according to claims 10 or 11 wherein the coating agent is a co-polymer of polymethacrylic acid and acrylic acid esters that is soluble in intestinal juice from pH 5.5 upwards.

30 13. A dosage form according to claim 12 wherein the release-delaying substance is present in an amount of approximately 2 to 30% (w/w) relative to the uncoated dosage form.

35 14. A delayed-release oral dosage form comprising cimetidine or a pharmaceutically acceptable acid addition salt thereof and optionally a buffer that is capable of generating a pH in the range 3.5 to 6 in a 1% aqueous solution, coated with a release-delaying substance in an amount of 2 to 30% (w/w) relative to the uncoated dosage form, the release-delaying substance comprising:

	<u>% (w)</u>
40	Coating agent                        40 to 100
	Plasticiser                            0 to 20
45	Lubricant                             0 to 40
	Film disintegrating agent            0 to 40

50 15. A dosage form according to claim 14 wherein the coating agent is Eudragit<sup>R</sup> L or L 30 D, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate or polyvinyl acetate phthalate or a mixture thereof.

55 16. A dosage form according to claim 14 wherein the coating agent is a copolymer of polymethacrylic acid and acrylic acid esters that is soluble in intestinal juice from pH 5.5 upwards.

17. A dosage form according to any one of claims 14 to 16 wherein the cimetidine is in the form of its hydrochloride.

18. A dosage form according to any one of claims 14 to 17 which comprises a buffer that is capable of generating a pH of 4 to 4.2 in a 1% aqueous solution.

19. A dosage form according to claim 18 wherein the buffer comprises a mixture of monosodium citrate and disodium citrate.

5      20. A multi-phase medicament comprising an immediate-release phase containing cimetidine or a pharmaceutically acceptable acid addition salt thereof and at least one delayed-release phase comprising a dosage form according to any one of claims 1 to 19.

10     21. A multi-phase medicament according to claim 20 wherein the immediate-release phase comprises cimetidine hydrochloride.

15     22. A medicament according to claims 20 or 21 wherein the immediate- and delayed-release phases are combined in a single dosage form.

23. A medicament according to any one of claims 20 to 22 wherein the delayed-release phase and immediate-release phase are present in a ratio of 5 : 1 to 1 : 1.

20     24. A medicament comprising a delayed-release dosage form as defined in any one of claims 1 to 19 and a further therapeutic agent which is in a form which enables it to be released in the stomach.

25     25. A medicament according to claim 24 wherein the further therapeutic agent is an antacid or a stomach mucosa protective agent.

**Claims for the following Contracting States : ES and GR**

26     1. A process for preparing a delayed-release oral dosage form comprising cimetidine or a pharmaceutically acceptable acid addition salt thereof, which comprises coating the uncoated dosage form with a release-delaysing substance which does not permit more than 10% release of cimetidine after 2 hours in 0.1 N hydrochloric acid and which satisfies each of the following dissolution tests (a) to (c) in a European Pharmacopoeia apparatus, with rotating paddle, 100 revolutions per minute, at 37°C with 800 ml of buffered aqueous dissolution medium comprising sodium hydroxide and 0.04 moles of monopotassium phosphate :—

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		Conditions	% Release of Cimetidine	
5	T	After 2 hours in 0.1 N hydro- chloric acid and a further time in dissolution medium at pH 5.7, 6.0 or 6.8	Formulae with Cimetidine base	Formulae with a pharmaceutically acceptable acid addition salt of cimetidine.
10	E			
15	S			
20	T			
(a)	5.7	Minimum 85% after 2 hours	Not applicable	
25	(b)	6.0	Minimum 75% after 1 hour	Minimum 75% after 2 hours
30	(c)	6.8	Minimum 90% after 45 mins.	Minimum 80% after 45 mins.

2. A process for preparing a delayed-release oral dosage form comprising cimetidine or a pharmaceutically acceptable acid addition salt thereof and a buffer that is capable of aiding dissolution of cimetidine in the intestine, which comprises coating the uncoated dosage form with a release-delaying substance which does not permit more than 10% release of cimetidine after 2 hours in 0.1 N hydrochloric acid and which satisfies each of the following dissolution tests (b) and (c) in a European Pharmacopoeia apparatus, with rotating paddle, 100 revolutions per minute, at 37°C with 800 ml of buffered aqueous dissolution medium comprising sodium hydroxide and 0.04 moles of monopotassium phosphate :

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T	Conditions	% Release of Cimetidine
E	After 2 hours in 0.1 N hydrochloric acid and a further time in dissolution medium at pH 6.0 or 6.8	Formulae with cimetidine or a pharmaceutically acceptable acid addition salt thereof and a buffer.
(b)	6.0	Minimum 50% after 2 hours
(c)	6.8	Minimum 85% after 1 hour

3. A process according to claim 2 wherein the buffer is capable of generating a pH in the range 3.5 to 6 in a 1% aqueous solution.

4. A process for preparing a dosage form according to claim 2 or 3 which comprises a pharmaceutically acceptable acid addition salt of cimetidine and a buffer that is capable of generating a pH in the range 4.0 - 4.2 in a 1% aqueous solution, which comprises coating the uncoated dosage form with a release-delaying substance which does not permit more than 10% release of cimetidine after 2 hours in 0.1 N hydrochloric acid and which satisfies each of the following dissolution tests (b) and (c) in a European Pharmacopoeia apparatus, with rotating paddle, 100 revolutions per minute at 37°C with 800 ml of buffered aqueous medium comprising sodium hydroxide and 0.04 moles of monopotassium phosphate :-

T	Conditions	% Release of Cimetidine
E	After 2 hours in 0.1 N hydrochloric acid and a further time in dissolution medium at pH 6.0 or 6.8	Formulae with a pharmaceutically acceptable acid addition salt of cimetidine and a buffer.
(b)	6.0	Minimum 60% after 2 hours
(c)	6.8	Minimum 90% after 1 hour

5. A process according to any one of claims 2 to 4 wherein the buffer comprises citric, tartaric, benzoic or sorbic acids, alkali metal salts thereof, alkali metal phosphates or mixtures thereof.

6. A process according to claim 5 wherein the buffer comprises a mixture of monosodium citrate and disodium citrate.

5 7. A process according to any one of claims 2 to 6 wherein the amount of buffer is between 0.01 to 5 moles per mole of cimetidine.

8. A process according to claim 7 wherein the amount of buffer is between 0.1 to 0.5 moles per mole of cimetidine.

10 9. A process according to any one of claims 1 to 8 wherein the cimetidine is in the form of its hydrochloride.

10 10. A process according to any one of claims 1 to 9 wherein the release-delaying substance comprises a coating agent selected from methacrylic acid copolymers, polymeric methacrylates such as Eudragit® L, E, S, RL, RS, L 30 D, NE 30 D, RL 30 D, RS 30 D or mixtures thereof, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, ethyl cellulose or polyvinyl acetate phthalate, or mixtures thereof.

15 11. A process according to claim 10 where the release-delayed substance comprises :

20		<u>% (w)</u>
	Coating agent	40 to 100
	Plasticiser	0 to 20
25	Lubricant	0 to 40
	Film disintegrating agent	0 to 40

12. A process according to claims 10 or 11 wherein the coating agent is a co-polymer of polymethacrylic acid and acrylic acid esters that is soluble in intestinal juice from pH 5.5 upwards.

30 13. A process according to claim 12 wherein the release-delaying substance is present in an amount of approximately 2 to 30% (w/w) relative to the uncoated dosage form.

14. A process for preparing a delayed-release oral dosage form comprising cimetidine or a pharmaceutically acceptable acid addition salt thereof and optionally a buffer that is capable of generating a pH in the range 3.5 to 6 in a 1% aqueous solution, which comprises coating the uncoated dosage form with a release-delaying substance in an amount of 2 to 30% (w/w) relative to the uncoated dosage form, the release-delaying substance comprising :

40		<u>% (w)</u>
	Coating agent	40 to 100
	Plasticiser	0 to 20
45	Lubricant	0 to 40
	Film disintegrating agent	0 to 40

50 15. A process according to claim 14 wherein the coating agent is Eudragit® L or L 30 D, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate or polyvinyl acetate phthalate or a mixture thereof.

16. A process according to claim 14 wherein the coating agent is a copolymer of polymethacrylic acid and acrylic acid esters that is soluble in intestinal juice from pH 5.5 upwards.

55 17. A process according to any one of claims 14 to 16 wherein the cimetidine is in the form of its hydrochloride.

18. A process according to any one of claims 14 to 17 which comprises a buffer that is capable of generating a pH of 4 to 4.2 in a 1% aqueous solution.

19. A process according to claim 18 wherein the buffer comprises a mixture of monosodium citrate and disodium citrate.
- 5 20. A process for preparing a multi-phase medicament which comprises bringing into association an immediate-release phase containing cimetidine or a pharmaceutically acceptable acid addition salt thereof and at least one delayed-release phase comprising a dosage form as prepared in any one of claims 1 to 19.
- 10 21. A process for preparing a multi-phase medicament according to claim 20 wherein the immediate-release phase comprises cimetidine hydrochloride.
- 15 22. A process according to claims 20 or 21 wherein the immediate- and delayed-release phases are combined in a single dosage form.
- 20 23. A process according to any one of claims 20 to 22 wherein the delayed-release phase and immediate-release phase are present in a ratio of 5 : 1 to 1 : 1.
- 25 24. A process for preparing a medicament which comprises bringing into association a delayed-release dosage form as defined in any one of claims 1 to 19 and a further therapeutic agent which is in a form which enables it to be released in the stomach.
- 30 25. A process according to claim 24 wherein the further therapeutic agent is an antacid or a stomach mucosa protective agent.

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## EUROPEAN SEARCH REPORT

Application Number

EP 90 31 3123

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. CL.5)
A	WO-A-8 203 795 (A.M. METHA) * Claims 1-5,10; page 5, lines 29-31; page 12, lines 1-2,19-21; page 14, lines 21-22,26 * -----	1,10,12 14,20- 21	A 61 K 31/415 A 61 K 9/22 A 61 K 9/24 A 61 K 9/32 A 61 K 9/36
A	IL FARMACO, vol. 39, no. 3, March 1984, pages 67-75; U. CONTE et al.: "Press-coated, zero-order drug delivery systems" * The whole article, in particular page 68: "Experimental" * -----	1-2,5,9 -10	
TECHNICAL FIELDS SEARCHED (Int. CL.5)			
A 61 K			
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	08-02-1991	SCARPONI U.	
CATEGORY OF CITED DOCUMENTS		T: theory or principle underlying the invention E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons R: member of the same patent family, corresponding document	
<input checked="" type="checkbox"/> particularly relevant if taken alone <input type="checkbox"/> particularly relevant if combined with another document of the same category <input type="checkbox"/> technical background <input type="checkbox"/> non-written disclosure <input type="checkbox"/> intermediate document			